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ECHINOCOCCUS MULTILOCULARIS INFECTION

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The investigation of alveolar hydatid disease of man had its beginning more than a century ago, when Virchow (1855) reported that certain cases of apparent malignancy of the liver were caused by the invasive growth of a larval cestode of the genus *Echinococcus*. In recognition of the unusual morphological characteristics of this larval cestode, Leuckart (1863) applied to it the name *Echinococcus multilocularis*.

For about a century following Virchow's discovery, the specific identity of this cestode remained controversial. Many investigators, among whom Dévé and Dew were especially prominent, believed that alveolar hydatid disease resulted from the anomalous development of the larval *E. granulosus* (Batsch, 1786). As recently as 1953, Dew supported this concept in his discussion of variation in the development of the larval *E. granulosus*. Other workers, among whom Posselt was outstanding, were convinced that alveolar hydatid disease was caused by a distinct species of *Echinococcus*. Posselt defended this hypothesis in a large series of published papers, but his findings were generally not accepted. Among the more recent proponents of Posselt's dualistic concept were Henschen and Bircher, who stated (1945) that the cestode causing alveolar hydatid disease differed from *E. granulosus* in the dimensional proportions of its rostellar hooks, and in the form of the gravid uterus.

In 1949, the writer undertook the investigation of hydatid disease in Alaska, where *E. granulosus* was found to have a wide distribution. It was soon recognized, however, that another species of *Echinococcus* existed on St. Lawrence Island, in the Bering Sea (Rausch, 1952; 1953). This cestode differed morphologically and ecologically from *E. granulosus*, which does not occur on St. Lawrence Island. Moreover, it was determined that the larval cestode caused alveolar hydatid disease in man. This cestode was described by Rausch and Schiller (1954) as *E. sibiricensis*, and it was believed to be conspecific with that causing alveolar hydatid disease in Eurasia (Rausch, 1952; Rausch and Schiller, 1956).

The findings in Alaska led Prof. Hans Vogel, of the Nocht Institut für Schiffs- und Tropenkrankheiten, to undertake anew the investigation of alveolar hydatid disease in Germany. In the Schwäbische Alb, where the disease is endemic, Vogel (1955) discovered a cestode morphologically and ecologically identical with *E. sibiricensis*. He pointed out at this time that Leuckart's name had priority, should it be confirmed that the cestodes were conspecific. Through detailed experimental studies, and the comparison of adult cestodes collected from canine animals in Alaska and Germany with those obtained by feeding material of human origin to dogs, Vogel (1957) established beyond doubt that *E. multilocularis* is the cause of alveolar hydatid disease in man. It was also determined that the Alaskan and European forms of *E. multilocularis* differ in minor details of structure, host-specificity, and pathogenicity; consequently, Vogel (1957) proposed that the Alaskan form be regarded as a subspecies of the European species.

Some workers appear reluctant to accept the conclusions outlined above. Poole (1957: 427) stated: «The type of hydatid found in wild rodents was called alveolar hydatid, but it bears no resemblance to the human alveolar type.» He did, however, express the opinion that «There is a probability that this parasite is different from that usually associated with dogs, herbivores and man as found in Canada.» Leikina (1957) reviewed the status of the problem in the Soviet Union and considered premature the conclusion that *E. sibiricensis* and *E. multilocularis* are conspecific, although she agreed that *E. sibiricensis* is the cause of alveolar hydatid disease in man. Leikina's attitude stemmed from failure to understand the relationships of multicystic larvae from ruminants, a point which has also confused other workers (cf. Dew, 1953).

It is the purpose of this paper to summarize briefly the information available on the bionomics of *E. multilocularis* and on the disease it produces in man. The literature on this subject is voluminous, and space permits the citing of only a few of the most relevant references here.

HOST-RELATIONSHIPS OF *E. MULTILOCULARIS*

In nature, a canid and a microtine rodent are required for completion of the life cycle of *E. multilocularis*. Some of the more important hosts are species which have a circumpolar distribution.

In North America. — The arctic fox, *Alopex lagopus* Linnaeus, is the most important final host of *E. multilocularis* in Alaska. Naturally infected red foxes, *Vulpes vulpes* Linnaeus, have been collected (Rausch, 1956), but the difficulty with which they are infected experimentally indicates that they are relatively unimportant. Naturally infected dogs have been found on St. Lawrence Island. It has been determined experimentally that the cestodes develop normally in the wolf, *Canis lupus* Linnaeus, and in the grey fox, *Urocyon cinereoargenteus* (Schreber), but they have not been found to produce eggs in the coyote, *Canis latrans* Say.

The larval cestode has been recorded from two species of microtine rodents on St. Lawrence Island. These are the red-backed vole, *Clethrionomys rutilus* Pallas, and the tundra vole, *Microtus oeconomus* Pallas. Thomas *et al.* (1954) and the writer have also found infected shrews, *Sorex tundrensis* Merriam, on St. Lawrence Island. Infected rodents have not been observed on the mainland of Alaska, although the strobilar stage has been collected there (Rausch, 1956). Alveolar hydatid disease has been diagnosed in an Eskimo from Kotzebue, however. Several species of rodents have been infected experimentally in Alaska.

In Eurasia. — On Bering Island, near the coast of Kamchatka, Afanas'ev (1941) found *E. multilocularis* in both arctic foxes and red-backed voles. Farther south, Ishino (1941) collected an infected vole, *M. oeconomus,* on Simushir Island, in the Middle Kuriles. On Rebun Island, Ambo *et al.* (1954) found an infected cat, and Yamashita *et al.* (1955) collected the cestode from dogs. Using material of Alaskan origin, Yamashita (personal communication) successfully infected the following species of rodents: *Clethrionomys rutilus mikado* (Thomas), *C. rufocanus bedfordiae* (Thomas), *Microtus montebelli* (Milne-Edwards), *Meriones unguiculatus kurauchii* Mori, and *Apodemus g. geisha* (Thomas).

In Siberia, *E. multilocularis* has been reported from an Azerbaidzhan fox, and from an arctic fox on Kil'din Island (Leikina, 1957). Cestodes differing morphologically from *E. granulosus* were recorded also from foxes in the Omsk Oblast'. According to Leikina, larvae of *Echinococcus* have been found in red-backed voles from the Viliuisk region of the Iakutsk ASSR, and in a vole, *M. oeconomus*, from the Barabinsk region of the Novosibirsk Oblast'. Spasskii *et al.* (1951) recorded larvae from muskrats, *Ondatra zibethicus* (Linnaeus), from Kzyl-Orda and from the Kurgansk Oblast'. The latter were described specifically as alveolar. Vsevolodov (1953) made a detailed study of a muskrat having a generalized alveolar infection; this animal had been collected by an expedition of the Zoological Institute of the Academy of Science, Kazakh SSR. Spasskii *et al.* (1952) reported *E. granulosus* from 50.9 percent of 51 red foxes, *Vulpes v. daurica* Ognev, from the region of Lake Baikal. In view of the conclusions of Matoff and Jantscheff (1954) that *E. granulosus* does not develop normally in red foxes, these cestodes might have been *E. multilocularis*.

In Germany, Vogel (1955) found *E. multilocularis* in 4 of 11 red foxes from the region of the Schwäbische Alb, and the larvae in 4 of 260 voles, *Microtus arvalis* Pallas. Vogel (1957) also infected experimentally several species of microtine rodents indigenous to central Europe.

THE DISTRIBUTION OF *E. MULTILOCULARIS*

IN NORTH AMERICA. — Surveys thus far completed indicate that *E. multilocularis* is distributionally restricted in Alaska to the tundra zone. It may occur in arctic Canada, but this has not yet been determined. According to Miller (1953), cestodes of the genus *Echinococcus* have been collected from an arctic fox on Banks Island. Gibbs (1957) discussed the role of rodents in the epidemiology of hydatid disease in the Mackenzie River basin. He examined some wild rodents, but his work consisted mainly of unsuccessful attempts to infect such mammals experimentally with the eggs of *E. granulosus*.

James and Boyd (1937) reported a fatal case of alveolar hydatid disease in a 54-year-old resident of the Province of Manitoba. Although this man had immigrated from Iceland at the age of 7 years, it is possible that this was an autochthonous infection.

At the present time, the apparent absence of *E. multilocularis* from the United States and Canada cannot be adequately explained, since conditions for the survival and perpetuation of this cestode appear to be favorable.

IN EURASIA. — *E. multilocularis* was introduced on Bering Island with voles from the Siberian mainland (Stejneger, 1884; Barabash-Nikiforov, 1943; Johansen, 1950). It probably was introduced in the Middle Kuriles with foxes from Bering Island, and became established on Rebun Island following introduction of red foxes from the Middle Kuriles (Rausch and Yamashita, 1957).

E. multilocularis is widely distributed in the Soviet Union. Semenov (1955) reported a case from as far northeast as the region of Nizhne-Kolymsk. Leikina (1957: 150) stated that human infection «... is registered in West Siberia, in some regions of East Siberia, mainly in the Iakutsk ASSR, in Tartar and Bashkir ASSR and in separate regions of Kazakhstan, in other words, in the northeast section of the Soviet Union.» Pavlovskii (1946) stated that cases are observed annually in Irkutsk. There are also records in the literature of the occurrence of the disease much farther to the west (Henschen and Bircher, 1945).

In Europe, human cases have been diagnosed in northern Switzerland, in the French Jura, and throughout southern Germany, including especially Württemberg, Baden, and Bayern. According to the literature, *E. multilocularis* seems to be rare or absent in eastern Europe.

The approximate geographic distribution of *E. multilocularis* in North America and Eurasia is shown in Fig. 1. The few reports of alveolar hydatid disease in other parts of the world have not been considered here.

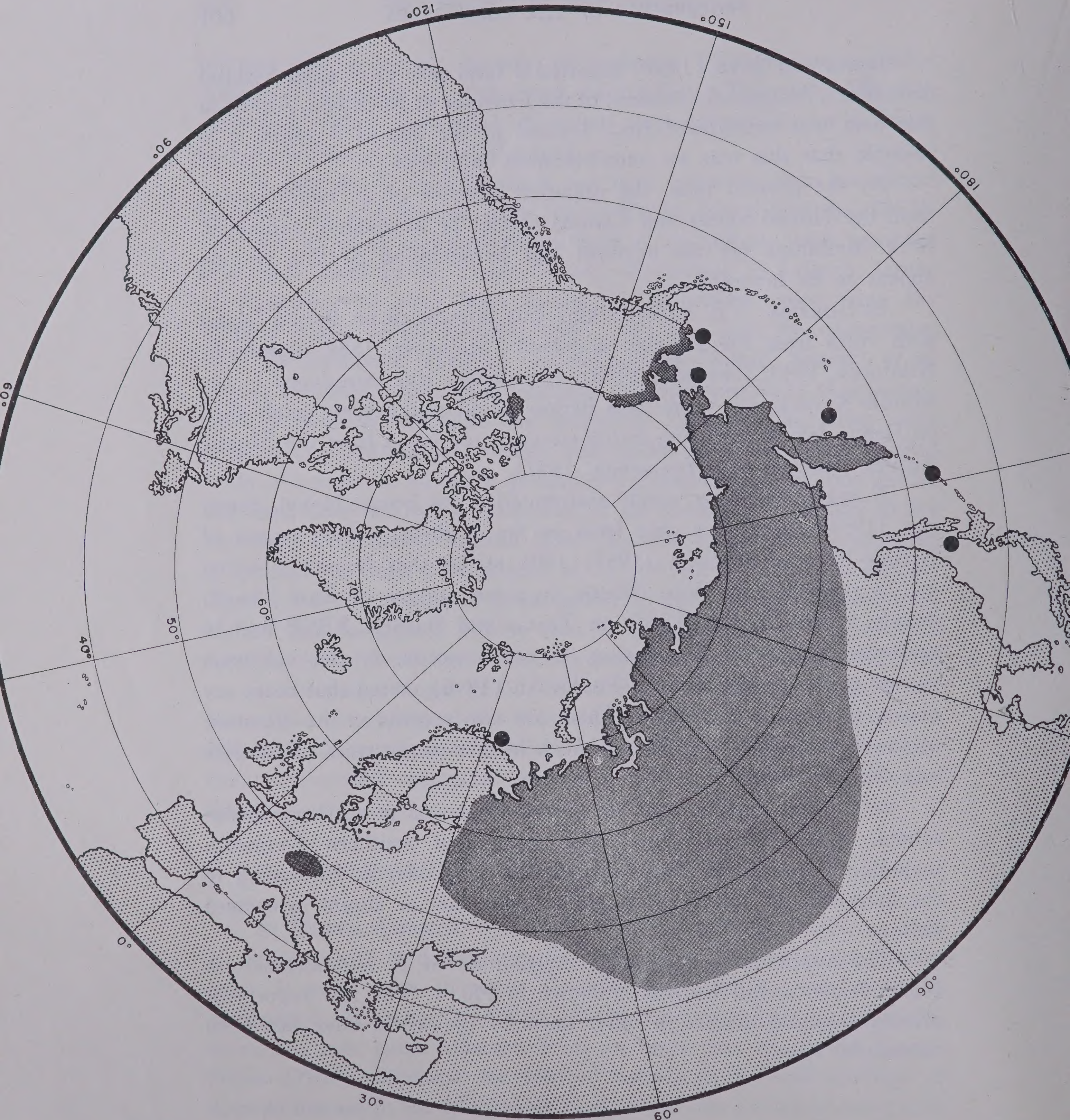

Fig. 1 — Approximate distribution (dark areas and circles) of *Echinococcus multilocularis* based on records in the literature

EPIDEMIOLOGY

In agricultural regions the natural cycle involves voles and foxes, but cats and dogs may replace foxes as the final host. Human infections may result when fruits and vegetables contaminated by the feces of canine animals are consumed. Close association with infected cats and dogs is especially dangerous. Yamashita (1956) expressed the opinion that contaminated water supplies might be an important source of infection on Rebun Island.

In northern regions, including Alaska and northeastern Siberia, infections may result from the careless handling of foxes which are trapped for their fur. However, it appears that the infection may be transmitted most frequently from sledge dogs. In Eskimo villages in Alaska, these dogs are very numerous and the environs of such villages are always grossly contaminated by their excreta. Eggs are undoubtedly brought into dwellings on soiled implements and footwear.

ALVEOLAR HYDATID DISEASE IN MAN

PATHOGENESIS. — After escaping the eggs in the small intestine, the onchospheres of *E. multilocularis* penetrate the intestinal wall and make their way to the liver by means of the portal circulation. In experimentally infected voles, the larvae penetrate the walls of the interlobular veins and enter the hepatic lobules, where growth begins (Rausch, 1954). The early stages of larval development in man are unknown. The larvae proliferate by exogenous budding, but the rate of growth in man appears to be much slower than in the natural hosts. According to Yamashita *et al.* (1955), the first human cases on Rebun Island were diagnosed about 12 years following the introduction of the parasite.

The liver is the organ most commonly affected in man. Dardel (1927) studied 102 cases in Switzerland, and found that more than 90 percent of these were hepatic infections. His comparative data on the localization of *E. multilocularis* and *E. granulosus* are summarized in the table here included. In the liver, the degree of pathogenicity is to a considerable extent related to the location of the infection.

When the larvae are more peripheral and superficial, the effect is less severe than when they are situated near the major bile ducts and blood vessels.

According to Posselt (1931) and Henschen and Bircher (1945), the right lobe of the liver is most commonly involved. In advanced hepatic infections, the pathological changes evoked are essentially those characteristic of portal hypertension. It is not unusual for the parasite to invade the gall bladder, the bile ducts, the larger blood vessels, and other organs. They sometimes rupture into the abdominal or thoracic cavities. When blood vessels are invaded, metastatic distribution of larval elements may result. Dardel (1927) observed 10 cases of metastasis when the primary infection was in the liver; 7 of these

A comparison of the localization and pathogenicity of the larvae of E. multilocularis *and* E. granulosus *in man* [1]

Locus of infection	*E. multilocularis* Number of cases : 102	*E. granulosus* Number of cases : 100
Liver	95	78
Lungs	1	9
Spleen	1	5
Kidneys	1	1
Brain	2	—
Bone	1	—
Abdominal wall	1	1
Ovary	—	1
Peritoneum and omentum	—	2
Parametrium	—	1
Thyroid and neck	—	2
Outcome	Number of cases : 102	Number of cases : 100
Died	84	35
Treatment successful	2	43
Unknown	7	1
Found accidentally at autopsy	9	21

[1] After Dardel (1927).

were in the lungs, and 3 were in the brain. Primary foci other than in the liver are rare.

Man is a relatively unsatisfactory host for the larva of *E. multilocularis,* for, as the larval mass increases in size, the central portion dies and undergoes degeneration, and only the peripheral layer in close contact with the tissue of the host is able to survive. This peripheral layer continues its invasive proliferation, and usually encloses a large cavity containing purulent material and debris. The larval tissue consists mainly of subgerminal elements; few or no scolices are produced in most human infections.

The pathogenesis of alveolar hydatid disease has been discussed in detail by Posselt (1925; 1931), Henschen and Bircher (1945), and others.

SYMPTOMATOLOGY AND DIAGNOSIS. — *E. multilocularis* infection gives rise to a chronic, afebrile disease characterized by hepatomegaly, and with icterus and ascites in the terminal stages. The clinical signs are in general those typical of intrahepatic portal hypertension.

The earlier stages of hepatic infection appear to be more or less asymptomatic, although there are exceptional cases in which deterioration of physical condition is rapid. The appetite usually remains good, and the ability to work is little impaired. As the disease progresses, there is marked enlargement of the liver, enlargement of the spleen, ascites, and increasing icterus. In experimentally infected rodents, it is not unusual for the liver to increase in size until it comprises more than 50 percent of the total body weight before normal physiological functions are much affected. In man, the liver is usually quite hard in consistency. Clinically, it is difficult to differentiate alveolar hydatid disease from carcinoma of the liver. Several investigators have stated that an unusually high sedimentation rate (40 mm and more per hour) is characteristic of this disease. The clinical diagnosis of alveolar hydatid disease has been discussed recently by Henschen and Bircher (1945), Vogel and Minning (1952), and others.

Röntgenological diagnosis is sometimes possible if calcification has occurred (Friedrich, 1940). The calcified areas usually have a reticulate or granular appearance in röntgenograms.

Immunological tests have commonly been applied as an aid to the diagnosis of this disease. The Casoni intradermal test and the complement fixation test have been most frequently used, but there is disagreement as to their reliability. Henschen and Bircher (1945) considered the intradermal test to be more accurate than the complement fixation test, but pointed out that false positive reactions are sometimes obtained. Using an antigen prepared from alveolar larvae, about twice as many positive intradermal reactions were obtained among Eskimos on St. Lawrence Island as were obtained from the complement fixation test using fluid from *E. granulosus* cysts for the antigen (Rausch and Schiller, 1956). More recently, Dr. G. F. Otto and his coworkers attempted to evaluate the significance of the relatively high rate of positive reactions obtained among Eskimo and military personnel on St. Lawrence Island. Using antigens prepared from alveolar larvae and from cyst-fluid, including fractions of the latter, it was found that a relatively high rate of positive reactions was obtained by both methods. When the two tests, using the same antigens, were applied to a control group of unexposed military personnel in the United States, a similar high rate of positive reactions was noted (Otto *et al.;* unpublished data). Hence, at the present time, it appears that these tests are not reliable for the diagnosis of alveolar hydatid disease.

Dr. I. G. Kagan and his coworkers (unpublished manuscript) have recently completed an evaluation of the hemagglutination and flocculation tests in the diagnosis of hydatid disease. They concluded that both methods are superior to the complement fixation test, but the hemagglutination test is the more accurate. Additional work is needed to determine the value of this latter test in the diagnosis of alveolar hydatid disease.

At times, even the *post mortem* diagnosis of alveolar hydatid disease is difficult, and pathologists unfamiliar with it are liable to make incorrect diagnoses. The latter is especially true in the United States, where the disease has been rarely observed. Vogel and Schumacher (1957) found that the periodic acid-Schiff reaction stains the larval membranes an intense red; this method makes possible the recognition of small vesicles and thin membranes which otherwise could be overlooked.

TREATMENT. — The curative treatment of alveolar hydatid disease consists of the surgical extirpation of the portion of the liver or other organ involved. Such treatment is often practicable during the earlier stages of the infection, but advanced cases are usually inoperable. Much depends upon the location of the infection. When the major bile ducts and vessels are involved, or when multiple foci exist, resection is usually impossible. The best results are obtained when a single mass is so located as to permit a partial hepatectomy.

Most cases are far advanced when diagnosed, and the prognosis is then quite unfavorable. Of 25 cases from Rebun Island, 15 terminated fatally (Rausch and Yamashita, 1957). Semenov (1954) reviewed 152 cases treated by surgeons in the Soviet Union. Of these, 108 (71 percent) were inoperable; 21 terminated fatally after surgical treatment; at least 12 were considered to have been cured. The remainder either refused surgery, or the outcome was unknown. In addition to these, Semenov personally treated 65 cases; excepting one case in which the spleen was involved, all were hepatic infections. Forty-two cases were inoperable, and 2 patients died following exploratory laparotomy. Twenty patients had radical surgery; 15, including the one with the infected spleen, recovered, and 5 died. Thus, treatment was successful in about 24 percent of the cases. Dardel (1927) reported 102 cases; 84 terminated fatally, 2 were successfully treated, the outcome on 7 was unknown, and 9 were found accidentally at autopsy.

Surgical procedure in the treatment of alveolar hydatid disease of the liver has been discussed by Hosemann *et al.* (1928) and by Henschen and Bircher (1945). In other organs, surgical procedure is similar to that required for the local extirpation of a malignant tumor.

PREVENTIVE MEASURES

Alveolar hydatid disease in man can be prevented at the present time only by the establishment of hygienic practices effective in precluding the ingestion of the infective eggs of *E. multilocularis*. Since the infection of man takes place only through direct or indirect contact with animals in which the adult cestodes occur, the appropriate control of dogs and cats is especially important. An anthelminthic efficacious against *E. multilocularis* in such animals is not known at present.

In conclusion, it is emphasized that further research is required (1) to gain a better understanding of the epidemiology of alveolar hydatid disease to allow the development of adequate preventive measures, (2) to produce an anthelminthic effective against the adult cestode in dogs and cats, and (3) to develop techniques which would permit the diagnosis of this disease in man early enough for successful treatment.

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